ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

BREAKOUT GROUP DISCUSSION - RUMINANTS

THURSDAY, FEBRUARY 24, 2000

8:30 A.M.

DOUBLETREE INN

1750 Rockville Pike

Rockville, Maryland

Regency Room

I N D E X

BREAKOUT GROUP DISCUSSION - RUMINANTS

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Keynote: "---" indicates inaudible in the transcript.

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(8:40 a.m.)

DR. RIDDEL: Okay. I guess we should get started. I appreciate everybody's help and your indulgences yesterday trying to get me up to speed.

I think what I need today is -- I really don't foresee my role going down a list of question and answering them one-by-one in my presentation this afternoon. I look at this as trying to put, from the ruminant aspect, our best foot forward as to coming up with a workable solution.

Something that will satisfy public health concerns, CVM's concerns, and the industry's concerns as well the target animal species' concerns for helping derive a pre-approval set of studies.

And so I have got a couple of questions that I need to ask -- that will again, to educate me like several I asked yesterday -- but I think I would like to hold those until the end.

I am going to need input from people today, just to make sure we cover all the bases. Right now, in as short a period of time as we can, but as long a period of time as it takes, to go down through that set of questions that we have.

And I think that while -- you know I am new to this and I have always heard people talking about CDC said this and

a CDC proponent's saying this, and our industry's being very reactive to that. Last night at a dinner I was cautioned about using the F word as being not appropriate. That would be Fred.

But, I think that there are some things that were thrown on the table that we need to maybe not respond to, but we need to make sure that we have our ducks in a row as far as answering concerns that if we don't answer them they are going to come back and bite us.

So, I don't know if you have your list of questions there, but we will do -- I was talking to a couple of the other species groups and they did proceed down through the questions and I may have gotten us off the track and not kept us as focused yesterday as I ought to.

And I thought I had some questions answered and in reviewing, I found out that ignorance is bliss and I was a lot happier before the few things I learned yesterday afternoon.

I guess the very first thing is, and again this to me from the outset has been a confusing question. It may be that it doesn't require much of anything, but what are the positive aspects of study concepts presented?

I assume that everything that we have heard up until just after noon yesterday, those would be study concepts. What kinds of things can we take from materials presented that could be positively used to help construct not a proscriptive, but at

least guidelines for information needed for products before they come to the approval process?

You all can't be slow starters again today. I used all the tricks I had yesterday. We just can't do this again. Okay.

DR. GOOTZ: Tom Gootz, Pfizer. It is a good suggestion you have made of going down the list, but it seems to me to some degree to be reiterating the discussions that we got into yesterday.

I am wondering, this is an alternative suggestion, to try to get as many positive and consensus things out of this as we can. Which I think is your goal as presenting our thoughts as a group.

Can we just -- I think you have 20 bullets there (indicating), is that correct? Twenty pieces of information.

MS. HARPER: Yes.

DR. GOOTZ: Maybe we should just, rather than go through, sort of open up the discussion, just go through those and see if we can distill some of those down to bullets.

A much smaller group of points and then as we do that, I mean some of these are going to be open-ended so that we just won't be able to reach an agreement. But, as we pare those down then address the questions on that set.

In other words, have we satisfied questions one,

two, three, four, and five by paring down and coming up with a list of conclusions or specific statements from the group. Do you think that might be an acceptable way to proceed?

CO-CHAIRPERSON HESLIN: Could we ask the group?

A suggestion has been made as an alternative way to approach addressing these questions. Does anybody have any comments on the approach put forward? Does that sound like something that would be workable this morning?

Keeping in mind that I think Gatz may be feeling the pressure that he has got to have something here by the end of the morning for the presentation this afternoon. So, we can go with this approach of revisiting the bullets within the context of the questions?

(Audience is nodding yes.)

DR. GOOTZ: I have one more question to clarify. Is this the only things that have been written down or that will be entered into our discussion and our generation of this list of bullets that you will present?

I mean we have been writing I think -- no, you have been writing stuff down cause there has been so much said yesterday. What we of course want to do is as a group make sure that we are all working from the same list so that our contributions, whether they are well accepted or not, will be the final sort of list of talking points or bullets.

So is that reasonable and agreed to that what we now will work on is just that list?

DR. RIDDEL: I will be quite honest, and this makes no inferences to our scribe, but the way I look at that list is that that is a bunch of random thoughts that probably defies organization into our bullet points.

I think we probably need, if we are going to come up with the bullet points of things we are going to put into the presentation, we have a lot of information but to construct that we are going to have to start from ground zero.

Again, that is no negative --

DR. GOOTZ: Okay. That is fine. Again, that is what we are trying to stay away from today is yesterday. It was very complex, a lot of good things said, endless number of issues brought up. But I guess as long as we can use mainly this and any other specific comments as talking points, that that is what will end up on the final set of bullets that you will take forward.

DR. RIDDEL: Can we agree, and I have got a couple, very few, introductory comments coming down. But to me the overriding factors, dependent upon perspective, and we probably in this environment need to take the perspective of public health first.

We have to make sure that whatever we do we can have

basic assurances that public health will not be threatened. Two, I think industry and practitioners, and regulatory agencies too, but especially to look at my perspective as a practitioner, we have got some really good tools to treat BRDs, but its one of those things where, taking the first precept into consideration you can't have too many tools in your armament.

So, we would like to see more products come to market for two reasons. Should that stop, we are limited on tools and we are not assured a supportive role by the pharmaceutical industries in the future. Because once that pipeline shuts down it is going to be very hard to crank it back up.

So, those are some pretty important concepts for me. And the bottom line is industry, to maintain their role as a player has to be assured that there are realistic, logistically feasible hoops that they can jump through to get the products to the end user, meaning the producer, that we need.

And now there are some introductory comments that I would like to order and say these are the points that we need to base all of our discussions on because if we don't do any of those three, if any of those three falls out, the whole thing falls apart.

So I think we need to consider how we look at pre-

approval studies and how they may factor into any of those three issues, under those three issues.

DR. GOOTZ: But, if that is presented as a framework, I guess what I am hearing you say is basically you are looking for a framework that will allow you to incorporate what is already be discussed and the notes everyone's been taking over yesterday, to make sure all of the points of view are reflected here.

DR. RIDDEL: I have got another step I would like to take so we can kind of get on the same page.

DR. GOOTZ: Sure. I mean that is why we are here. I think today we are trying to build a house and we have to have components that a house -- got to get it done by 11:00 o'clock, it has to pass safety codes, we all want to be able to live in it.

All I am saying is that the blueprint for that house is up there (indicating) or somewhere in this room. But, when the blueprints are put on paper as bullet slides, my only point, sort of a point of order, is that we are going to agree on final bullets here. And that is what your going to -- we may not agree, obviously, and that is fine.

I mean you can reject all of the things that we put forward. That is not my point. My point is though that in this session this morning, we are going to come to one list of

bullets that come from this group. And then it will be brought forward.

It may not be accepted. Our goal as a group is to make sure that the house is sound, but the house still may not sell. So, do you follow me in terms of how we are going to do it?

DR. RIDDEL: Sure.

DR. GOOTZ: Okay.

CO-CHAIRPERSON HESLIN: But, I don't think it is a question of being accepted. I think whatever the group has to say, and it is said here, is the information that is going to be passed forward.

MR. FLYNN: It is another way of answering the questions.

DR. RIDDEL: Bill, were you going to say something?

MR. FLYNN: Yes. I was just going to comment. First off too, remember that everything is being recorded in all of the rooms so all of the comments are being recorded so nothing is going to be missed from that standpoint.

The purpose of this was really just to get some of the main ideas up there. And although the questions that were provided in the agenda, they may not be the best questions in the world or be a complete list of questions, we wanted some sort of common threads so that when the four groups got back

together again their was some common points that we could sort of compare across the board.

So, if we could try -- and I don't want to be limited to just those questions. But if we could try to be able to from each of the groups get some feedback on each of those questions. Then we would have some way of comparing different opinions across the different groups.

DR. RIDDEL: But we don't have to go down one, two, three, four, and five? It can be incorporated in the body of our response?

MR. FLYNN: Yes. I think if you can identify -- as long as we are able to tease out of there where that question was addressed.

DR. RIDDEL: You have got to understand, I work in a university and our greatest tactic is confuse and conquer. That won't work here. I was hired under false pretenses.

MR. FLYNN: I mean it is up to you as to how you want to proceed. But if we could try to at least be able to get some response on those questions that are on the agenda to some degree so we can sort of compare notes with the other groups to see where opinions differed on certain items.

And then you can embellish as much as you like with other points that you think are important.

DR. RIDDEL: Okay. Now, Dr. Flynn, everybody else

had the task yesterday of trying to educate me. And while you are here, I will have to ask you to do that.

There are a lot of things I don't understand about the approval process. One of which is the concept of pivotal issues or pivotal points. Should for some reason all four groups propose that it is critical that each sponsor for every product they put forward has to have information relative to rate of mutation, whatever 10^{-8} means, and let's say that CVM accepts that as an acceptable tenet whereupon to base part of the approval process.

Will that become -- and this is for my edification -- will that therefore become a pivotal point and therefore be a pass/fail bar that they have to pass at some point in time? Or has is that used? That is just for me. Everybody here probably understands.

MR. FLYNN: I think the simplest definition that I can think of would be that basically if it is a piece of information that we said we need to have in order to make a decision for approving the product, then essentially it is pivotal for the package.

If it is just additional information that we could make a decision with or without then it is a non-pivotal piece of information.

DR. RIDDEL: I am assuming, that after probably the

most common comment that pertains to my next question, is that nobody feels that one-size fits all. In other words, we can't describe a prototype package for pre-approval studies that everybody can make any upcoming product fit.

How will the framework of the general concept pre-approval studies be viewed as needed information, extra information, pivotal or not?

MR. FLYNN: Well, I think the concept, and that is right I mean I don't think there is one study that fits all. And even the framework, the concept there is that not all applications would necessarily require the same level of information.

And I think I said in my talk that there may be certain applications that don't require any specific studies. So, it just depends on the particular use and class of drug.

So when you are thinking about the study it is not that this is one study that every application for an antimicrobial product to be used in a food animal would have to do that study.

I think we just want to open this up to what are all the different -- what types of information would be helpful to try to address the question. Then we would have to get into the stuff: when is it necessary to apply that? When do we need to use that piece of information.

DR. PETRICK: Yes. Dave Petrick from Schering-Plough. Bill, I will ask you and maybe some of the other folks from CVM here. Now industry obviously has had a lot of discussions about this and how do things fit and where are they as part of the approval process.

And, I guess what I would look at is some of the things that I am getting out of this. And again, as not being a microbiologist, but it just strikes me that there is certain information that we can collect that for an antibiotic seems like it is something the Center would want to have at some point in the review process.

I guess we can, or at least I am not getting the sense from what the microbiologists are saying, that it can be much more pre-approval other than either kind of the idea of a benchmark or information that should be there at the start of the process to help with the post-approval monitoring aspects.

So, when I look at it from my point of view or my perspective of regulatory affairs, the question I always think of is how does that fit in the process? And where does it go? One of the things that I was turning over in my mind last night, it does relate to the pivotal/non-pivotal aspects of this.

It seems to me that since we seem to be coming up with the idea that this is data whether it is MICs or mutation

ability or mechanism of resistance development, that pre-launch all you can do is say this is where it is right now. You can't put it in the concept of pass/fail.

If you do that, one of the things that I can think of that it sort of fits with, is the batches that we run at the site of manufacture, pre-launch. In other words, validating the process at the site of manufacture. Well, you don't really need that pre-approval, but you have to have it pre-launch.

I think in some aspects this data are the same kind of concept we are dealing with here now. I think in this case it is going to come very early on because the sponsor is going to want to know this information early on in the process.

But, I think it is almost not that it is pre-approval, it is sort of pre-launch materials that we need to have to assist in the post-approval monitoring. I think we saw a lot of interesting things in the last day and one-half of studies that could be run, studies that are under way.

And we seem to be collecting a lot of good information, but I don't think the body of knowledge is there right now to be able to say it is predictive of what the course of resistance development is going to be.

So I think if you look at it in that context and trying to put that into the framework of approval, I think what I look at is there is information there that the Center may

want to require pre-launch, but that we don't necessarily as tied directly to the approval of the product from a safety and efficacy standpoint.

But it is something that the sponsor has to put forward so you can get into a good post-approval monitoring framework. I don't know if that makes sense procedurally, but in my mind it kind of seems like a good place to slot it in the process.

At least with where we are right now with the state of scientific knowledge that we have. And just Mr. Chairman, one point. I think from the way these things generally run, I think you want to be able to go through, at least in your mind, how the responses are to those five questions.

And the last question they give us an opportunity to say what other proposals would you make and I think that is where we can come up with the bullets of what we think we digested out of the five. But, I think it would be a good idea as Bill said, is to help the Center compile this. If we could still address maybe those five issues at some point or another. Even if they are addressed in a very, kind of simplified manner.

CO-CHAIRPERSON HESLIN: I still wonder whether the blueprint has been agreed upon. Because I am thinking that if there is this framework or blueprint to sort the comments

already and to have a home for additional comments so they don't just get lost in a running list of things.

DR. SHRYOCK: Yes. I would like to request that the scribe record Dave's comments. I think they are spot-on. If this is to be a pass/fail pivotal type of study, then the amount of extra study that is going to be required to establish in vitro as well as in vivo studies is tremendous. And probably will be rate-limiting.

So, I would like to request, whether it is slide 21 or up to 30, whatever it takes, to capture those comments. I think that is essential. If we then want to go through and talk about in vitro studies, there is quite a number that we could begin to discuss, pro and con, limitations, bugs, answering these questions.

We can do that. And I think what we will come up with is that these will not be predictive. They will be highly variable. They will be tremendously complex and of uncertain value. We can do that with the animal studies as well.

We can list all of those points if you want to spend the time to do that. I think we have got a great start with some of the speaker's presentations.

So, my suggestion would be that if we can decide how to use this information and it should be interpreted up front, whether it is to be pivotal or informational. And then if it

is informational or supplemental, whatever we want to call it, then we have got to rely on that post-approval surveillance system as the safeguard.

And that is yet another workshop to be held, I am sure. So that would be my suggestion. If we get this pivotal issue up front and then we can go into in vitro studies, list a bunch of those out, pros and cons. Do the animal studies, pros and cons. That should take us through the discussion.

DR. RIDDEL: I would like to point out as you make these comments, you need -- everybody should understand where I am coming from. For me to get up and talk about pivotal studies and in vitro studies and in vivo studies is a joke. And so we are going to have to couch things in a framework that I can have some credibility to get up there and make comments.

Because I don't have the background to talk about a lot of things that you all talk about. Period.

MR. HALLBERG: John Hallberg from P&U Animal Health. I guess what I go back to is a suggestion I made yesterday in that we need to provide information. And it will be "pivotal" is suppose that we, as a company, bring forth mechanism of action of the antibiotic, in vitro potential for resistance generation, either literature or in vivo ideas of cross-resistance.

And then use our understanding of compound

metabolism, PK/PD to define a good efficacy plan. Have an idea of baseline MICs for the target pathogens and some of the select zoonotics. And then have a definition of "sensitive" for MIC testing in the future.

And then what this allows us to do is to define a plan to use a new compound, and this is a truly compound based thing. It is not one-size fits all.

So, if we come in with a beta-lactim, a macrolide, or a fluoroquinolone it is going to be compound-dependent. And then at the end of the day you are going to sit down with the agency and work out a plan on how to set up the post-approval monitoring.

But, basically no compound is off the table when they come in the door because in theory, from what was said, if you can show a proper use of this compound that does not generate adverse effects in zoonotics or potential human resistance on human therapeutics, then that compound should go forward.

So, I am proposing that after seeing everything that went on yesterday and I will open that up for discussion.

DR. SHRYOCK: Tom Shryock again. Slide 21 is getting better, but we need to really do a lot of wordsmithing on this.

MS. HARPER: Okay.

DR. SHRYOCK: Okay. So, let's start that process. In vitro pre-approval studies should be informational and non-pivotal.

MS. HARPER: Okay.

DR. SHRYOCK: That would be my suggestion. Comments from the group?

DR. PETRICK: Tom, why don't you put in there a sentence as to why you believe that to be so.

DR. SHRYOCK: Okay. The reason this should be informational is because the studies, both in vitro as well as in vivo -- in vivo studies being pathogen load, and in vitro resistance selection -- are highly variable. They will not be predictive of protecting public health.

And the need to establish baselines for post-approval surveillance can replace these studies. Comments?

DR. PETRICK: I think that is the answer to the first question.

DR. SHRYOCK: Okay. That is good.

DR. RIDDEL: He's going to take over.

DR. SHRYOCK: No, no.

CO-CHAIRPERSON HESLIN: If that is the answer to the first question, would it be helpful to list the questions and sort this information that is appropriate to the question so there is some framework for presenting it this afternoon?

DR. GOOTZ: Tom Gootz, Pfizer. Can I make a suggestion?

CO-CHAIRPERSON HESLIN: Sure.

DR. GOOTZ: It might sound a little dumb, but it might work. As you are scribing here, now we focused -- thank God down -- on a very specific issue. Can you italicize that bullet so we link it with question number one?

We may need two, three or more bullets that are all linked to question number one. I think we are making progress here.

First of all, --

MS. HARPER: Is that okay?

DR. GOOTZ: Yes, that is better ideas. So we will stay focused like a laser beam as the president says on the first issue as to question number one.

I would like to -- and don't write this down in terms of adding to Tom's bullet. But I would just like to say that hopefully the ultimate goal in pre-approval studies as many people have said is to establish a very good, hopefully credible scientifically-based information or baseline of microbiology data from which post-surveillance studies that Bob has suggested and talked about, can spring from.

So, where was the drug with respect to it is potency against field isolates before it was approved? A little bit

about mechanism of action. Mutation frequency, things like that. The four talking points that the CDC mentioned yesterday. And make that as information in the submission.

My point is, again you brought the pivotal versus required or informational issue, and that is very important. There probably would be a movement to make all of this stuff pivotal.

But, my comment is a lot of these things like microbiology or a PK number, an AUC, I don't see how that can be a pivotal thing. Who's to say that a compound with an AUC at a certain dose of X passes, whereas a similar compound with an AUC of Y against the same indication is okay?

On a level playing field, if that is the case then I think we should do as scientists. Do good microbiology studies to establish a baseline. That gives a lot of information. But I don't see how mutation frequency can be pivotal. I mean I really don't.

Number one, you are going to get one, so you will have a number. Hopefully more than one number looking at your key zoonotic pathogens that you are concerned about. We are all concerned about.

But I don't see how just setting down a yes or no approval as a pivotal study for a mutation frequency is really defensible scientifically or really has that much of a

precedence in the organization.

MS. HARRIS: Sorry. Mary Harris from Pfizer. I think that kind of goes to question number two: "What role does the data play?" And I think it is pretty clear that we think it is non-pivotal to an approval decision, but it is important information for establishing baselines for post-approval monitoring.

MR. WATTS: Jeff Watts, P&U. Just to kind of put a little different perspective on this. This is not one-size fits all for the simple fact that none of the companies that are working in this area are in the "me too" business.

Even if we are working in the same class of drugs, we are looking for a competitive advantage with our particular compound. So those compounds may break the rules to some extent. And so that is why we have to have some flexibility and you have to keep things open to allow for the different characteristics of drugs, even if they are in the same class.

CO-CHAIRPERSON HESLIN: Would it be helpful to go back through these comments and have these people decide which comments really go with which question?

DR. RIDDEL: Yes.

CO-CHAIRPERSON HESLIN: I was just going to suggest that at some point here maybe what we could do is go back through these comments that were made yesterday and so far

today and try to relate them to a particular question. To put some form and structure to this.

I think it would be helpful in terms of the presentation to make sure that the comments you are making are roughly related to the questions and it is categorized in that way. Does that sound like a reasonable thing to do? Go back over the list?

DR. SHRYOCK: Not yet.

CO-CHAIRPERSON HESLIN: Not yet. But at some point?

DR. SHRYOCK: Maybe later.

CO-CHAIRPERSON HESLIN: Yes, at some point. So you still just want to generate the comments at this point and then go back?

DR. SHRYOCK: I think maybe it would be helpful -- we have got some momentum going here on some of these potential pre-approval studies. Maybe if we go through some of those we can talk pros and cons that are the questions that we need to address.

And we will back fill that way, then we can go back through slides 20 through number 1.

CO-CHAIRPERSON HESLIN: Okay.

DR. GOOTZ: Tom Gootz from Pfizer. To that end, then I guess keeping like on bullet number 22, it mentions what a pre-approval study should have in it, what it should include.

You have mechanism action, which is great. We discussed that. Some assessment of cross-resistance. That is great.

Mutation frequency, compound metabolism, PK/PD, baseline MICs, a definition of sensitivity -- there you mean susceptibility, hear my ears susceptibility instead of sensitivity.

And at the end of that sentence just for clarity, I think we are talking about both field isolates and a reasonable number of zoonotic pathogens. Aren't we?

DR. PETRICK: No, target organisms.

DR. GOOTZ: Oh, sorry. Target organisms and some zoonotic pathogens.

DR. SHRYOCK: NARMS isolates.

DR. GOOTZ: NARMS isolates.

DR. RIDDEL: The concept of having susceptibility studies for target organisms is not a public health issue, right? That is an efficacy issue?

DR. GOOTZ: It is. PK/PD could be considered that too. Again, I think what we are trying to do is bring a body of information to CVM to characterize the compound. Because that was something that was mentioned yesterday several times.

We as sponsors are supposed to characterize the compound. And as was pointed out a minute ago, even compound mechanics within a class hopefully are going to have some

pretty different characteristics.

So, while some of these things don't necessarily address the safety, it gives you we think a better picture in total of what the compound is and what we hope it will do in respect to efficacy.

So, other things that could be compound mechanic specific, we might determine levels under the metabolism, levels of drugs in feces. And also the degree of binding of the drug to fecal matter. Since that is sort of the PK area with the zoonotic pathogens that you are concerned about.

And just a piece of information, without the extensive studies, just some idea of what the levels are there.

Somebody yesterday pointed out, I think it was from the CDC, that in the zoonotic pathogen group. And we will just use E. coli since it always seems to be genetically the best characterized. That it might be useful to look at susceptibility of the new product against genetically defined zoonotic pathogens, meaning E. coli.

With the idea of getting understanding in a known genetic background, with one resistance mutation to the class. Let's say it was quinolones, after the standard Chart A type of mutation. What that does in terms of the MIC? Again, that is all pre-approval. It is a baseline of understanding.

So, the idea was -- and this can be a separate

bullet -- some limited testing and genetically defined zoonotic pathogens that have known mutations in them.

Again trying to move forward on some of the microplates. Other people probably have --

DR. SINGER: Randy Singer, University of Illinois. I don't know a lot about what industry currently does for instance assessing cross-resistance and mutation frequency, but I can see that written that way, in a very general and loose fashion it could end up being a real weighty exercise.

If you had to go out and look, almost in a monitoring effort, for every mechanism that might exist that would confer cross-resistance or any kind of mutation that you can't induce in vitro but that might already exist and can be transferred in confer resistance. Some might interpret those ideas, assessing cross-resistance and mutation frequency as a major endeavor.

And so I am not sure, without really specifying clearly what that entails, I am not sure anyone would want to get into that mess.

DR. WALKER: Bob Walker, FDA. When you are determining the baseline MICs and definition of susceptibility, I think one of the things that needs to be tied very, very close to that is the quality control guidelines or quality control ranges for your compounds against quality control

organisms.

An example of this is it is my understanding that florfenicol was taken off the NARMS list because there is no interpretive criteria for E. coli on it. And so if you had the quality control organisms and the ranges for those organisms then you can validate your MICs and generate your susceptibility data. But without that there would be the potential for considerable variation from laboratory to laboratory.

CO-CHAIRPERSON HESLIN: Your earlier comment about one of the statements up here being rather broad-based and a concern about that. Is there some alternative language or something else that needs to be up there?

DR. SINGER: For now maybe it works because this is simply a bullet list. I am just thinking in the future as a working document it could end up being a real open-ended type of study that the industry would have to do to get the drug approved.

DR. SHRYOCK: Just to follow-up on Randy's comment and use Tom's analogy here. Maybe we are deciding what kind of house we do want to build today. And maybe we have decided that we want a two-bedroom instead of a four-bedroom house.

This probably will mean we are all coming back to Rockville, Doubletree for another meeting to perhaps define

some of these particular general types of studies in a better way from a microbiological or animal science perspective.

I think perhaps that is beyond our immediate charge today, so perhaps as a sub-bullet within 22 that we should have something to the effect that further discussion and definition of these particular types of studies will be required.

And, as a component of that a literature review would be implied or necessary. Because I think there is a lot out there that we don't have to go out and find new genetic mechanisms of resistance for macrolydes for example. There is plenty of them out there. How hard would one have to look when there is already a plethora of information out there.

CO-CHAIRPERSON HESLIN: But further study, for purposes of this list, would capture it?

DR. SHRYOCK: I think that would suffice on my end, yeah. I would certainly open -- and it is way beyond us to talk about how we are going to mutation frequency studies in a few hours today. There are so many variables. But we can decide those kinds at a later time.

DR. SINGER: Randy Singer. One thing that I think would be useful since the post-approval process for one drug directly would influence the pre-approval of a following one would be maybe for FDA-CVM to be the one to maintain some sort of database that keeps apprised of what the new, what the

literature reports in terms of new genetic mechanisms identified for resistance, etc.

Because that would influence how post-approval monitoring is done as well as what types of systems need to be addressed for a pre-approval study in a future situation. But having some uniform database of what is out in the literature as well as maybe what doesn't make it into literature I think would be useful.

Maybe that is just again being naive at this point. But I think it would be useful.

DR. RIDDEL: The final endpoint of any approved product, as far as determining when mitigation steps have to be taken will be the post-approval monitoring program.

And in that regardless of what compound you put up, the nearest pertinent human antimicrobial is the test product for susceptibility/zoonotic pathogens in the NARMS program? In other words, they don't use enrofloxacin, they use ciprofloxacin?

Is there any validity, since this work's going to have to be done anyway, of entering in a blinded fashion a product into this program before it is approved so you are generating data and you make a smooth transition into the post-approval monitoring program?

You identify this as the type of compound you'd have

to put out information -- relative to that if you are going to give it characteristics, metabolism beforehand and since you don't have to use the exact product, then proprietary information may not be a stumbling block.

Could that be entered into, obviously it is not post-approval, but could that be a pertinent, relevant information gathering system that is going to impact it? And if the product is not being used, you are really just collecting baseline data until it hits market. Right or wrong?

(People nodding yes.)

DR. RIDDEL: Unless there is some other fact or some other antibiotic which is causing resistance patterns to that class of antibiotics.

I was just wondering, because that came to me last night and I figured it was really naive.

DR. GOOTZ: Tom Gootz, Pfizer. That sounds reasonable. I am just wondering though if there are a lot of new products coming on line or at least being submitted, put it that way, would NARMS have the capability of adding sort of all of those that would be in development?

And if they are limited -- again, I have no idea. This would be their issue. If they were limited in any way would then that stop timely introduction of a new antibiotic into that system? I don't know.

DR. RIDDEL: But, that baseline data is going to have to be collected somehow, right?

DR. GOOTZ: Well, NARMS has a large database obviously for the fresh field isolates which is what we would be doing in industry. The concept sounds reasonable. I am just wondering if they would agree to putting them in.

And whether that is the correct vehicle for us to college that data. I don't know.

DR. RIDDEL: Well, if for example another fluoroquinolone was being considered, would they have to change what they are doing if they are using ciprofloxacin as the test antimicrobial for evaluating resistance to those pathogens?

DR. GOOTZ: No, it could be -- I thought you said you wanted them to try to add your drug to our drug -- maybe I misunderstood you.

DR. RIDDEL: Well, I guess I was reading something last night that they don't add your drug, they add -- they do add your drug?

DR. GOOTZ: No, I am agreeing. That is right. They use cipro.

DR. SHRYOCK: It is cipro. Perhaps -- Scott's here he could probably tell us all about this.

It is feasible to do what you are suggesting Gatz, but the logistics in there may be a little tricky. It may be

sufficient that that would be one of the things that we would want to further define within the use of NARMS data.

For example, if a new product is going to be used in poultry, you go and you request as a sponsor X number of poultry isolates over a period of years to get a baseline. And you test those strains in-house. Alternatively, if it is a compound of a similar class you could just look at the data.

In order to insert a new chemical entity into a NARMS panel, it is my understanding that it would take at least a year's lead time if it even fits logistically within a 96 well panel. And there are some constraints there.

And why should sponsor A be favored over sponsor B if you only have one slot? There are some potentially technical issues along those lines that could ensue.

So perhaps just using those isolates in some fashion would suffice to get the kind of information pre-approval that we need if it is a new class or one that is not currently being evaluated. Just as an alternative idea.

Scott, I will put you on the spot if you care to be on the spot.

DR. EWERT: Good morning. This is Kathy Ewert from Bayer Animal Health. Just a follow-up to what you are saying there Gatz.

The problem that I can see with the NARMS panel

right now for example with cepholosporins or with fluoroquinolones would be if a new generation of those products came on to the market which is what is happening now. We are into fourth generation fluoroquinolones.

And those products for example have a broader spectrum of activity and a different set of MICs would be generated for those compounds. Different breakpoints, excuse me would be generated for those compounds over ciprofloxacin.

And so then at some point the NARMS panel may be changed from ciprofloxacin to a fourth generation fluoroquinolone that is being used more commonly. And it might be unfair to compare a fourth generation fluoroquinolone with ciprofloxacin that is on the market as a third generation fluoroquinolone.

So I think that is a dynamic process that could change. And one of the things that I mentioned in my presentation was that perhaps we should look at more than one drug within the class. Because even though you confer cross-resistance, that resistance is at a different level.

Fluoroquinolones -- within the class you can see resistance, but there is different levels of resistance and so that needs to be addressed somehow.

CO-CHAIRPERSON HESLIN: Any other comments? I am sorry, you needed something clarified?

MS. HARPER: Yes. The last comment, I don't know if I captured it correctly. Could you look at that?

DR. EWERT: I am sorry?

CO-CHAIRPERSON HESLIN: The last comment, whether that reflects in essence what you said.

DR. EWERT: No, I didn't say it may not accurately reflect. I said it may be necessary. And that more than one compound within a group may be necessary to accurately reflect what is going on. Do you agree with that, Tom?

DR. SHRYOCK: Yes. I think that is a positive ---

MR. LADELY: Scott Ladely, USDA. I don't think we need to dig into this too deep because it is burning our time.

What we are currently doing is we have 17 spots on a plate. That is a big limitation. We are not looking at macrolides at all because we don't have enough spots on the plate.

Every year they are evaluated. We try to represent animal and human drug classes that are currently being used. We maybe need to look at doing more than one plate for each isolate.

They are evaluated annually and adjusted. Maybe we need to drop off some of the older drugs that have resistance because we know they have resistance.

But we need to move on to discuss these other issues

instead of the flaws in the current monitoring system.

CO-CHAIRPERSON HESLIN: Any other comments? I think there are a few folks here we haven't heard from in the last day and one-half or so. So, if you have some perspective or some input, feel free. This is your opportunity.

(No response.)

CO-CHAIRPERSON HESLIN: Is this then the point to go back through the list?

DR. RIDDEL: I guess go to the top of the bullet points and we can just --

CO-CHAIRPERSON HESLIN: Yes, I think we are going to do that, but the question is do it now or later and I am not hearing any other comments. That is why I am wondering whether it is now.

Do you all need time to talk among yourselves about some of these issues?

DR. GOOTZ: I don't know. There are other issues that you mentioned that you want to move on to. Do you want to be any more specific?

MR. LADELY: --- what we are doing as far as monitoring ---

DR. GOOTZ: I know.

CO-CHAIRPERSON HESLIN: Can you suggest our next step to move forward? What would you like to discuss next?

MR. LADELY: Back to the list. Try to work them out.

DR. GOOTZ: Well, let's do this --

CO-CHAIRPERSON HESLIN: Maybe by revisiting the list that is going to expand the discussion as well. Can you shoot up to the top?

I guess what we are doing here is looking at these earlier comments or suggestions trying to, maybe if necessary, force fit them to a particular question and making sure the comment is reflected the way you want it reflected as a group. And if there is a minority view or whatever we can add it as well.

What question would this first bullet be related to?

DR. VAUGHN: This is Steve Vaughn at CVM. Let me try to help this a little bit. The first three bullets get to that and I think slide 21 that Tom wordsmithed are really the first parts of this.

CVM needs to have what would be considered pivotal information submitted in the pre-approval phase of drug development. That information would be used to make a decision as to whether or not there was an adequate basis to go forward to approval.

I think what we are hearing is that that information would not be predictive of whether resistance or loss of

susceptibility would reach a public health level or not. So rate and extent would be hard to do in a pre-approval decision.

But, nevertheless there needs to be information submitted upon which the center can make a pivotal decision as to whether it has adequate information to go forward with the approval of the product. And that speaks more to the completeness of the package then it does the predictive value of the content of the package.

So, if we can focus I think a little bit more on what needs to go into that package that would be of value, much of that information I think is already being generated by pharmaceutical companies in their discovery phase. And we take a look at that kind of information.

I think that really gets to the point of the five questions.

DR. EWERT: Kathy Ewert, Bayer Animal Health. There was a discussion in another group about pivotal versus non-pivotal studies and perhaps Steve you can give us the agency's take on what pivotal involves.

It is my opinion that if a pivotal study is submitted it has to be accepted by the agency prior to approval of that compound. Whatever the pivotal study is. For example, efficacy. There are certain criteria that the agency looks for for acceptance of those studies and acceptance of that phase

component.

This is what we are looking for, is some kind of direction. If indeed we have to do these studies, what are the factors that the agency sees need to be evaluated so that we can move forward.

DR. VAUGHN: Well Kathy, you missed the point. Bill, before you came in, defined pivotal.

DR. EWERT: Oh, I am sorry.

DR. VAUGHN: And to the extent, just to reiterate it, pivotal is merely a term that we use. It is nowhere in the law or the regulations. It is just a term that we use that is information upon which we will make a decision about the approvability of a particular product relative to its safety and effectiveness.

Now, what kind of decision we make doesn't make it pivotal or non-pivotal. I hope we don't get hung up on that. It is pivotal in the sense that we need to be able to say we have an adequate basis to ensure the safety and effectiveness of the product in the post-approval environment.

And what the scientists here are telling us, as I am hearing it and you guys can correct me certainly, is that the kind of decision that would be unacceptable would be one that would be predictive.

On the other hand, the kind of pivotal decision that

we would make is there adequate information in the file that this product can move into a post-approval environment.

But there needs to be a pre-approval package and what are the elements of that package or the attributes of that package? And that may include studies of various kinds that give us the kind of information that builds that base of information.

DR. GOOTZ: Tom Gootz from Pfizer. Just a clarification. If we didn't submit anything for the compound that would be pivotal in the sense you would say there is nothing in the document, therefore our pivotal judgment is to refuse to accept the compound, right?

So we are going to put things in the submission, we are going to do studies. We are going to try, I think, as sponsors to do good microbiology studies. Ones like described generally on Tom's slide.

The problem I am having, maybe because I am missing the point, is you guys keep saying pivotal and in our minds that means that there is a quantitative link to it. A better way is data should be, and what we have done which should address the pre-approval issues for you, industry and the League of Concerned Scientists and congress, is that we are going to put together a very good package of microbiology data including pharmacology data like for PK.

All of these things we generally mentioned. And you could call those supportive studies. You could call those the types of the studies that you would require for competence and good faith to review a package. Which is what they say in the human health side.

And you may want to ask us to do more stuff because of the pressure you are getting from all of these other groups with respect to the concerns over zoonotic pathogens. Which we will certainly try to do that and put those in that package of studies that are called required.

But, unless I missed the point, and I probably have, the word pivotal to us implies a heavy burden in the sense that there is a quantitative assessment to it. It isn't a term that we are used to thinking of in terms of well, you checked all the general boxes, we see things in the submission, so we are ready to go.

Pivotal to us means that if we say that cipro as an example frequency of resistance mutation in salmonella typhe and you name the strain, is under a standard test done in three different labs. If that mutation frequency is 1.5 to 2.5 times 10^{-8} and we, with our new same class compound, get a number that is 6.5 times 10^{-7}, a pivotal study would say thumbs down.

What the scientists have been telling you and some of your own folks and even the CDC yesterday are trying to tell

you that that type of microbiological data, you can use any word you want. It is not predictive, it is variable, it is this, it is that.

They are trying to tell you that there is not a black and white, yes or no data based on microbiology so why are we calling it pivotal? Why are we calling it pivotal because unless I am missing the point pivotal means pass/fail.

DR. VAUGHN: No.

DR. GOOTZ: No it doesn't?

DR. VAUGHN: No. Pivotal, and we are getting hung up on terminology here and we are not going to have a report for Gatz if we are done. Pivotal merely means that we are going to make a decision, we need that information to make a decision.

It doesn't say what kind of decision we are going to make. It doesn't mean it is going to be pass/fail. It doesn't mean we are going to go thumbs up/thumbs down. And that is the purpose of this workshop.

And part of the what information is of value? is one thing that we are trying to derive from this workshop. But it also comes with qualifications as what kind of regulatory decision can be made in a pre-approval mode.

Even though it is still pivotal, it is information we would require to be submitted. The type of decision comes

from the caveats and qualifications that you folks are giving us to put around that kind of information.

Does that help?

DR. GOOTZ: No.

DR. RHODES: Can you give us an example of an alternative decision that wouldn't be pass or fail?

DR. VAUGHN: I think, you know obviously we are going to need to have, and I can't say whether we will or not, but it is becoming obvious to me that we need a post-approval workshop to talk about what is the structure under which antimicrobials would be marketed.

That wasn't stretching very far at all was it? You don't want to do it. All right.

But, within that scheme we need to know what information is going to be important pre-approval. And whether or not we made a decision -- let me try an example. That might be the easiest way to do this.

For labeling we use in vitro microbiology information. We use pharmacokinetic information. The type of decision we make there: is it accurate, was it done in a fashion we believe they are real numbers. But do we say based on the blood level profile or the MIC data we are not going to approve that product? No.

So even though that information is pivotal for

labeling, it is not a decision where we say yes the product is approvable or no it is not approvable. But we are looking at the voracity of the information we are going to put on the label.

So there is different kinds of decisions that are made even though it is pivotal. So let's try not to get hung up on the term pivotal, but let's focus on what is the kind of information that is important to have and how should we use that information in a pre-approval regulatory environment.

DR. EWERT: Kathy Ewert, Bayer Animal Health. I think what we are all trying to envision as scientist here working in the development process is that we need to be able to focus on something and we have to have a finite end to this.

What I hear you saying, Steve, is that well you can submit this and this and this study and we will take it under advisement. And we will consider it and see if it meets our requirements. And I just feel like -- I have this recurring dream where I try to get somewhere and I can't get there. I mean -- really, I do have that dream.

And I am having that same sort of feeling. That well, we will meet this requirement but then another door opens and whoops, there might be something else we have to do. And I think what we are looking for, whether we call it pivotal or non-pivotal or required or whatever, we are looking for those

end points so that we say well, if we do this study and it satisfies the requirements, then we can move forward.

For example you used pharmacokinetic data. Well, that is a very quantifiable study and we know as companies that if our pharmacokinetic data isn't good we are not going to move ahead with development. We are certainly not going to submit it to the agency.

So I think -- anybody else want to chime in here? I think that is what we are looking for.

DR. PETRICK: Well, I will disagree with Kathy on this one.

DR. EWERT: Uh-oh.

DR. PETRICK: Because I think I understand what we are getting at here. In the context of if the study is reproducible, then it is a valid study. So, the label for MICs or the label for the C-max and the AUC is what it is. If it the study in the reviewer's mind is a fair representation of what would go on the label then you have met the criteria.

And it was pivotal from the concept of the fact that it was on the label. And the Center isn't going to allow it to be on the label unless they use that as part of their decision-making process. It is like the SBA on the human side. And it could appear in the FOI, there is no reason it couldn't. Because again, the Center used it as part of their decision-

making process.

So, I think if we go back to point 21 that we worked on, I think that is kind of what we are suggesting are the studies. So what we give as a sponsor is MIC data. What the Center says is well, was the MIC data generated accurately? Would it be reproducible? Is it done in the appropriate manner?

If the answer is yes, it is what it is and it is not a pass/fail criteria. It is just there. Just like the kinetic data. Was it done in a reproducible manner? Is it a fair representation of what the product is doing to target species? And if it is it is there, it is not a value judgment of it ought to be better or it ought to be higher or it ought to have a higher C-max or anything else. It is just there.

It is pivotal from the standpoint that it went into the decision-making process. And I think it is a decision-making process is it here or is it isn't here? So the pass/fail is nothing more -- and correct me if I am wrong -- but I think the pass/fail is nothing more, if we agree that for an antibiotic there ought to be MIC, there ought to be PK, there ought to be -- it is a question of it is present or it is absent and I think that is the pass/fail as opposed to it is a certain number.

Is that what we were --

DR. VAUGHN: --- caveat --- putting in the record if we feel that something should not be --- predictive decision.

DR. PETRICK: Right. And I think that is what we are getting at. I don't think anybody, at least from the discussions we have had in this room and then discussions we have had out of this room. It just strikes me that what we are getting at is no one saying we have got a predictive mechanism or predictive studies right now, but you can put these items out here and post-approval those items would help you make a decision.

So, it makes sense to us that they become there -- they are submitted and when we move on from there, post-approval, into the processes as you said what do we do down the road post-approval? Which is probably going to be the subject of another workshop.

I think it makes sense that you move ahead in a logical fashion. If we can get to the point where we say right now we are not science -- it is not we, but science isn't at the point where we can do model studies that are going to predict rate and extent of resistance development.

I just don't think we are there. I think there is a lot of good information that can be generated and interesting things to pursue scientifically, but I don't think there are things that we should be pursuing from a regulatory, pre-

approval standpoint.

DR. EWERT: Steve, I don't disagree with you at all.

CO-CHAIRPERSON HESLIN: Could you step to the microphone please when you speak, we are trying to get this recorded.

DR. EWERT: Kathy Ewert, Bayer Animal Health. I don't disagree with you at all. I think that is correct. But there is a finite amount of work that needs to be done and that is I think what we are looking for.

DR. PETRICK: Right, and I think that is point 21.

DR. EWERT: Okay.

DR. PETRICK: I think that is the list of studies -- I think that is what we are saying is the package of information that gets put in that either it is there or it is not there. Or, and we can go a step beyond going back to a comment over here.

You have a discussion with the Center that says for this compound, for these reasons it is accomplished in this manner. It isn't necessarily additional work because there is plenty of literature information that says this family of compounds does this. So the Center says yes, there is a literature reading that accomplishes that.

DR. EWERT: That is fine.

DR. PETRICK: Is that --

DR. GOOTZ: Tom Gootz, Pfizer. Just quickly. So, to cover bullet 21, the microbiology doesn't seem to be that new, quite frankly.

Has the agency always called that type of data pivotal? It is in the writing and that is how we have been responding to it as pivotal data. It is in your guidelines.

DR. VAUGHN: Well, once again I have yet to see it written, the word pivotal, in any of my documents. It is just a term of ours.

DR. GOOTZ: But you are using the term now --

DR. VAUGHN: As a basis of this information upon which we make a regulatory decision. ---

DR. GOOTZ: Okay. So a new term, kind of, has been introduced.

DR. VAUGHN: Or dismissed.

DR. GOOTZ: I move we dismiss it. And second. All those in favor? All right. Any opposed?

MR. LUCAS: Don Lucas, Roche. Dr. Vaughn, I would -- my recollection is that quite often studies are classified as pivotal or non-pivotal, particularly regarding efficacy. So it is not a term that is foreign at all to me. Certainly in the production area.

MS. HARRIS: Sorry, I didn't want to prolong the -- oh, Mary Harris, Pfizer. I don't want to prolong the pivotal

discussion. But, on top of pivotal and non-pivotal being used extensively in efficacy studies, outside production drugs too. There is a known set of guidelines or standards or criteria for those kinds of studies.

I think that is another big gap we face in how we are defining these microbiological data for the public health issue.

DR. SHRYOCK: Tom Shryock, Elanco. Perhaps to try to bring some of this pivotal/non-pivotal discussion back to our charge here, to address questions on slide 21. If we look at question 2, "What role could these various types of data play in evaluating microbial effects?"

Supposing we were to take this list of different studies and ask what role those could play to provide some guidance, context, whatever you wish to call it, for the Center so that they would be then able to make decisions about the data in some way. Knowing there are limitations to the data that is derived, that sort of thing.

Just throwing that out. Would that be a helpful exercise to complete? It would start then to address some of these specific questions, role, factors, pathogens, all of the rest of that. Just as a way forward, a suggestion perhaps.

CO-CHAIRPERSON HESLIN: Any reaction from the group on that?

MR. MUSER: Rainer Muser, representing myself again. I am not going to talk about pivotal, but in a way it will come back to it. It has been helpful in other areas to have a list of studies or standards, whatever, by which you can go.

And the usual practice, and correct me if I am saying it wrong, was if you wanted to deviate from it you would have to justify it. And gracefully, FDA sometimes if they wanted to do something different they have to justify it to industry, too.

I believe it might be helpful if we make sure that it gets recorded, what was said earlier. It would be helpful to have a list of studies or maybe standard protocols for whatever studies the experts, and I am not one of them, may come up with.

A list of studies and a list of study protocols that can be then used for providing the information that is needed. And if a company feels that a new antibiotic needs a different type of study, I am sure they could justify it and then it would be taking the place of one of the studies in the standard list.

I think that might help to cut through this discussion of pivotal and non-pivotal. Thank you.

DR. RIDDEL: By standard study, Dr. Muser, you mean the things that have been listed as far as having PK/PD data

and baseline MICs, those kinds of studies?

MR. MUSER: Yes. There ought to be a possibility for experts to agree on if I want to study any of these --- that are listed here, this is an acceptable protocol to do it.

DR. RIDDEL: I guess, again out of my ignorance, I have heard several people address this over the last four and one-half hours now. But those things are listed in point 22 that are relatively repeatable in your early evaluation of your product. Have fairly known protocols for how you perform those.

While they may not be totally predictive they give you a basis for understanding the potential for what a compound may behave like. And four, you have that information already. For the most part.

Okay. On the other hand, FDA-CVM says they want that information. I am having a problem with all of the time we have spent getting to this point. We have the information and that is what CVM wants.

Now, maybe they want us to say a lot of the in vitro models that were presented in the first day and one-half lacked predictability and therefore have no role in this at this point in time until a model can be presented that would be in the laboratory that operates under GLPs as predictable, repeatable, and valid as to an MIC data. Right? That is what you wanted?

If somebody were to define an animal model or a laboratory model that could take and evaluate an antimicrobial for its potential to in part reduce susceptibility to microbes of zoonotic potential, and it was predictable, repeatable, and had been validated, and was do-able. Then that model would be fine.

But, we have not been shown in the workshop to date, any such model.

MR. HALLBERG: Good point. And we can't wait for one at this point. We have got to move forward and get things moving.

CO-CHAIRPERSON HESLIN: We are scheduled for a break at 10:00 o'clock. Maybe we should end for now and you can continue your discussions among yourselves. We are going to reconvene at 10:30.

(Break)

CO-CHAIRPERSON HESLIN: There had been some discussion at break about focusing on certain aspects of information that has been generated so far. And I don't know whether that meant not covering the rest of it. Whether we should do a run through of all of the bullets, the comments, as sort of context and background, and then bring the focus down to particular slides for further presentation.

I think that is what Gatz is trying to do right now.

DR. SHRYOCK: We can run through the bullets and see how they slash out. I think we have got a good start on that.

DR. RIDDEL: Run through the bullets beginning with one?

DR. SHRYOCK: No, the one's you're going to present. The nice background ones. What was going on looked good.

DR. RIDDEL: Yes. I hate to waste your time while I am typing that stuff in. But, if we could -- here is what you can help me do.

If we can come to an agreement on some -- I think you all are pretty happy with what the pre-approval studies may entail. Which is -- what is on here is in text form, but I am going to put in bullet points and we can go through it.

Is there in any of these bullet points, are there caveats or addenda or points of information that should be added as we are presenting them?

MR. HALLBERG: Well, the one caveat would be is number one, pre-approval studies do not or are not available to predict the rate and extent of resistance development. Those don't exist today and we know it.

And that these pre-approval studies -- and I would maybe change the information that studies provided by the sponsors in a pre-approval setting should provide key information on the following list of information. And they may

include individual studies, they may be wrapped into one study. But that is for the sponsor to determine how it is.

DR. RIDDEL: Now, the best way to phrase this is "rate and extent of changes in microbial susceptibility" rather than saying "resistance" or what is the best way of saying this?

DR. PETRICK: I would say it exactly as you have it, just to respond to the specific question, resistance development.

DR. RIDDEL: I am sorry. Say it again?

DR. PETRICK: I would do it exactly as it says up there "rate and extent of resistance development" that is the discussion for the framework and the conference and I would stick with that.

And my colleague here says maybe and add pathogen load as well.

DR. RIDDEL: Well, shouldn't that be a -- since you don't have a rate or extent of change in pathogen load, but can you say the same thing for -- every group I talked to and the best information I can get out of my interpretation of what you said is that pathogen load studies are irrelevant in the pre-approval phase.

Or there are no models that can -- what is going to be the best way of putting that, because I don't think I can

add "and pathogen load" all at the end of that sentence.

DR. PETRICK: With limited value to addressing pathogen load.

DR. SHRYOCK: I think we had some of that wording on one of the prior slides, 21 or whatever it was, that suggested that pathogen load studies are not able to satisfactorily protect public health because -- however we had that worded before with the variability, the extrapolation. Whatever we had up there in 21.

DR. RIDDEL: In which point, Tom?

DR. SHRYOCK: I think it was slide 21. It was the one we started with this morning. Pathogen load, in vitro. That would be "These studies are highly variable and not predictive relative to public health" that would be the line. It could also apply to the pathogen load studies.

I wouldn't get into specifics as to why that is the case.

DR. RIDDEL: So, could you say pathogen load studies are highly variable and not predictive relative to public health? Leave the in vitro and in vivo?

DR. SHRYOCK: Take out the in vitro.

DR. PETRICK: Why don't we just strike it?

DR. RIDDEL: Strike the whole thing?

DR. PETRICK: No, no, no. You have it correct ---

DR. SHRYOCK: I would be stretching to come up with a way.

DR. PETRICK: I know ---

DR. SHRYOCK: It is redundant, I agree.

MS. HARPER: They want you to strike in vivo.

MS. HARRIS: If we are still on caveats, can I add a couple that Bill Flynn mentioned? That not all uses and classes of drugs require pre-approval studies.

DR. RIDDEL: Drugs or do we specifically say antimicrobials?

MS. HARRIS: That is fine.

DR. SHRYOCK: Antimicrobials. That is fine.

DR. PETRICK: But aren't we saying they should all have the same ---

MR. LADELY: If it is not for a human use. My understanding is that ---

(Group is talking amongst themselves while Dr. Riddel is working on the Powerpoint presentation - the microphones were not picking up enough of the conversations to transcribe.)

MS. HARRIS: --- Are we trying to say that CVM is not requiring something that we think is required?

DR. PETRICK: I am saying that if we are going to take the position that all antimicrobials should have this information, then I think we should be consistent. Or, we

should say that for most, or something.

That is all I am saying. I mean I don't ---

DR. EWERT: Let me ask you ---

CO-CHAIRPERSON HESLIN: No. I think this open discussion is better than coming to the microphone. I would just ask you to speak up a little bit to try to pick up the voice.

DR. EWERT: Just a question of clarification. I was under the impression that the framework document has been written and if within the framework document one of the requirements for drug approval was pre-approval studies, now the framework document is, CVM people, that is still a reality, right? That is not going away, is it?

So, if it is a reality then we need to work under the context of what CVM has already performed with the framework document. And that is a correct statement then, that not all uses and classes of antimicrobials require this.

Maybe we should say require the same pre-approval studies.

DR. EWERT: Right. For an example, --- this is an example from --- would need the pathogen load studies, whereas a single injection of therapeutic would not ---

So that has been delineated in the framework

document.

DR. RIDDEL: Is that good enough?

DR. SHRYOCK: The next slide should probably be what studies we would like to put forward.

MR. BIENHOFF: Also, is there someway of stating there that it is not necessarily --- some of these requirements?

DR. VAUGHN: You tell us.

DR. EWERT: That is an open-ended comment. I am not going there.

DR. PETRICK: Steve, I think he has got a point there ---

DR. VAUGHN: I don't read that --- is it up there?

DR. PETRICK: I know. It is a good point though.

DR. RIDDEL: Okay. The pre-approval studies may include -- no changes on this? Actually, which did you mention as far as this compound metabolism?

MS. HARPER: If you are in a ---

DR. RIDDEL: Then also leave degree and volume in there?

MS. HARPER: Yes.

DR. EWERT: By a definition of susceptibility do you mean breakpoints? So does that mean that we have to establish

breakpoints for non-target pathogens, for food-borne pathogens?

CO-CHAIRPERSON HESLIN: I am not sure he got all of that.

DR. RIDDEL: Well, I -- this is the list we came to as a consensus, and now we need a consensus or at least a valid opinion as to changing it.

MR. LADELY: You are going to have to monitor more of your target organisms.

MR. WATTS: Monitoring and doing MIC studies are one thing, but --- NARMS --- because interpretive criteria by definition ---

DR. EWERT: And we don't have --- food-borne pathogens.

MR. BIENHOFF: Can this be ---

DR. EWERT: You could say baseline MICs without interpretive criteria.

DR. EWERT: Gatz, just put interpretive criteria for target organisms. Everybody agrees with that?

MR. BIENHOFF: --- is this part of the process?

DR. SHRYOCK: That is actually, a lot of times --- breakpoints.

DR. EWERT: But, --- generated ---

DR. SHRYOCK: --- breakpoints for pre-approval?

MR. BIENHOFF: --- want that.

DR. SHRYOCK: --- could be sponsor options --- tentative breakpoints early on. ---

DR. EWERT: But then the NARMS pathogen has to be split out into another bullet ---

DR. RIDDEL: What do you want baseline MICs for? What should sponsors want to provide information to CVM in this arena as far as MICs?

DR. EWERT: That could be both target and NARMS pathogens.

DR. WALKER: I think that captures it.

DR. RIDDEL: Okay, and then how about ---

DR. WALKER: Are we generating this baseline MIC data or are you --- conditions?

MR. BIENHOFF: They should be generated under QC conditions and --- valid database.

DR. RIDDEL: Which one, here?

DR. EWERT: Yes.

DR. RIDDEL: Okay. Now, what do I need to do to modify this point?

MR. WATTS: Put a period after target organisms.

DR. RIDDEL: And delete the rest?

MR. : Move it down ---

DR. RIDDEL: Like that?

DR. EWERT: Just get rid of it, that part.

DR. RIDDEL: And you want this caveat also in there?

MR. BIENHOFF: Yes.

DR. RIDDEL: Anything else?

DR. EWERT: Can we add something in there that these studies may not have to be novel studies, but the information can be generated from literature. I will just defer that to everybody else in the room.

I mean if we are already dealing with a certain class of drugs, it seems foolish to repeat a lot of these studies.

MS. HARRIS: Can we shorten that to just say that pre-approval study data may be collected from ---

DR. PETRICK: And instead of saying studies you could just use information. Pre-approval information may not --- model studies.

DR. RIDDEL: Leave it at that?

DR. PETRICK: Wouldn't that cover it?

DR. VAUGHN: We don't want it coming out of Reader's Digest.

MR. : Would Hog Farmer's be okay?

DR. VAUGHN: Yes.

DR. RIDDEL: Leave it or not?

EVERYBODY: Leave that in.

DR. RIDDEL: Do you want to -- we have the first statement on the first slide about what things don't seem to work. Do you want to delineate those or just leave those as general statements?

I am going to have to tell a lot of jokes to stretch this out to 25 minutes guys.

Do you all see anything else?

MR. BIENHOFF: I suggest you go through the other bullets to make sure we are not missing anything.

DR. GOOTZ: You may want to pull some of those out.

DR. SHRYOCK: Did we want to try to capture any of our discussion? And I hate to bring this up again, but the discussion on how this information is to be packaged relative to informational purposes through support post-approval ---

DR. PETRICK: That might be the last bullet --- hold that thought.

If we could go back I think that maybe that is the conclusion point.

DR. RIDDEL: Does anybody see anything in the first five points that we need to incorporate?

MR. LUCAS: Is there opportunity to call this list?

Or is there a reason to call this list at this point?

MR. : I don't know.

MR. : Maybe if we look at these first three. They just catch my eye right off. That is a sort of repetition of the first day and one-half's questions that we heard presented in the presentations.

DR. RIDDEL: Yes. I guess that is what we are doing. This is a summation and comments of yesterday and this morning. What I would like to do is just go down through there and if there is some salient point that needs to go to the other -- the blue presentation is going to be the working document.

DR. GOOTZ: Yes, some of these that were questions, maybe we can try to craft them today. If we can't do that with some of them ---

CO-CHAIRPERSON HESLIN: And there might be value in keeping these here to show the range of discussion on some of these issues as well. Yes?

DR. VAUGHN: The last sentence in line number four I think is good advice ---

DR. SHRYOCK: Should we perhaps take that line out where they ---

DR. PETRICK: Is it appropriate to call these resistance studies? --- we are really talking about is the

information that makes sense for CVM to have. And I would hate for the MIC data to now be determined by a resistance study, or that the PK/PD ---

I think we are saying that that information is something that should get into CVM at an early stage.

DR. EWERT: How about if we say information supporting susceptibility ---

DR. PETRICK: Yes, I think that is a good point. ---

DR. GOOTZ: Are you after specific in vitro selection resistance studies ---

DR. EWERT: What we are just saying is that we need to do this early on ---

DR. PETRICK: Right. I think what we are saying is that this information should come into CVM early in the process. Not something that ---

DR. RIDDEL: That doesn't really belong. That statement, I understand where you are coming from, that doesn't belong in what we would propose to be what should be in pre-approval studies.

That is a cautionary statement to industry that this is an issue that you need to look at early on and develop your product. Wasn't that what you were meaning Steve?

DR. VAUGHN: No. Actually, I am looking at it as advice to CVM to consider this early on. This sequence, when

studies should be conducted --- talk about developmental plans. This is the kind of information and what I have heard a lot of people voice, is this information needs to go in early rather than later because of the potential impact on the --- pathogen --- it has been said enough times that --- this is something that should be sequenced early in the regulatory review process.

DR. SHRYOCK: Perhaps in the first slide under bullet three, --- maybe that would be an appropriate to put that because it is talking about not all pre-approval studies are required in all cases. That also puts the time sequence associated with that thought.

--- really what you want to do or not do.

MR. WATTS: --- you know the bottom line is a lot of this we will never see. If we have a compound that fundamentally has problems early on, the discovery team will ---

MS. HARRIS: Yes, but if you have this difference of opinion --- CVM ---

DR. EWERT: I agree. I think it needs to be done early because if there is a problem that the agency sees, that needs to be addressed.

DR. RIDDEL: Is that where "delayed" should be?

MR. : Just put these studies and get rid

of the word ---

MS. HARRIS: I think we ought to also put in, not just the development process but the regulatory review process.

DR. RIDDEL: Is this okay? Anything -- do you have an important item to be incorporated?

(No audible response.)

DR. RIDDEL: What about point 8?

MR. : The first part sounds good.

DR. RIDDEL: But, does the word and terminology threshold apply specifically to the post-approval --- program and any action based upon that?

Any information that you all come up with as far as the pre-approval study you say would be information you could see being presented in that package? Would they have any basis other than the baseline susceptibility studies, --- pathogens, for establishing thresholds?

Thresholds are going to have to be an agreement between the agency and industry as to what percent or what change is going to result in, and I am assuming but I could be wrong, that mitigation will be at various levels.

It wouldn't necessarily be that you are out of here the first time?

DR. VAUGHN: Gatz, I think 7 and 8 both ---

DR. RIDDEL: Pardon?

DR. VAUGHN: Both 7 and 8 --- some level of ---

DR. RIDDEL: Do you want that information to go before slide 3 where we start talking about pre-approval studies or do you want it to be informational material following those pre-approval studies?

MR. HALLBERG: Before.

DR. RIDDEL: Okay. Do any parts of this need to be changed, altered, or deleted?

MR. : --- as a separate bullet so that it doesn't get lost?

DR. SHRYOCK: I think we will ultimately come back to that even after our --- studies will be funded --- to the post-approval programs to be discussed. That is really the safeguard.

DR. RIDDEL: So, ---

DR. SHRYOCK: --- established with a threshold. I would take that out --- there is going to be a baseline of information generated, but we don't know --- threshold at some future date.

DR. PETRICK: With just the baseline.

DR. SHRYOCK: But you will have a baseline pool of information which could be used retrospectively --- but to say you have got X number and then --- Y. What does that mean? You can't do that pre-approval.

DR. PETRICK: You are establishing thresholds. Or should it be thresholds should not be established at pre-approval.

MS. HARRIS: Let me try this. Pre-approval studies should not focus on establishing thresholds. ---

DR. RIDDEL: Okay. I am sorry. If there is agreement on that can you tell me that again?

MS. HARRIS: Pre-approval studies should not focus on establishing thresholds.

--- something about baselines ---

DR. GOOTZ: The completed package in pre-approval studies will be used to establish baseline --- contribute to establishing baselines.

DR. RIDDEL: Establish baselines or thresholds?

DR. SHRYOCK: No, baselines.

DR. RIDDEL: What about the next sentence?

MR. HALLBERG: And then you can put "and design to help design the post-approval monitoring phase."

DR. RIDDEL: Is that phase or program?

MR. HALLBERG: Program.

DR. RIDDEL: Would or could?

DR. EWERT: Could.

DR. VAUGHN: Maybe useful in?

DR. PETRICK: I would say that gets back to the ---

DR. RIDDEL: Back to the document?

DR. EWERT: I have got a question on categorization. When are the drugs going to be categorized and by whom? Is this the company decision or is this the agency decision? When do we do that. I haven't heard -- I haven't seen anything about any drug categorized ---

DR. RIDDEL: Categorization is an important point, right?

DR. EWERT: Yes, categorization is because it drives what needs to be done.

DR. RIDDEL: Okay. If that is important, what do you want to put in there?

DR. GOOTZ: The sponsor will initially determine the categorization of the drug. Something to the effect, the sponsor would need to at a very early stage convey that to CVM or reach agreement with CVM ---

DR. RIDDEL: CVM?

DR. GOOTZ: Yes. You must somehow agree or something ---

DR. RIDDEL: Should it be pre-approval process or just process?

DR. SHRYOCK: Process.

MR. MUSER: I have a question for the experts. Is

it possible that pre-approval studies after they are available change the categorization? If so then it should be ---

DR. SHRYOCK: If it is possible to change the categorization. We haven't even had the discussion around all of the parameters of categorization.

MR. MUSER: I would like to change that to make it responsible. It might be good to have it.

DR. SHRYOCK: Yes. I think a lot of this is dependent on discussions we haven't yet had.

MR. MUSER: Right.

DR. SHRYOCK: As to how things shift or the caveats of low, medium, or high exposure. That all gets matrixed in there.

MR. MUSER: Right.

DR. SHRYOCK: And we are not there yet.

MR. MUSER: Right.

CO-CHAIRPERSON HESLIN: But, is that comment something that should be included in the slide?

MR. MUSER: I think it should be included.

DR. PETRICK: But what do we say? That we need to have a discussion next to assess categorization of new antimicrobials? I mean what is really the -- what is the crux that we are getting at here?

MR. MUSER: --- pre-approval studies and pre-

approval --- risk assessment. For --- risk assessment will lead to a categorization of the drug. And not the outcome of pre-approval studies.

But the information on the pre-approval studies would relate to potential resistance development of a resistance mechanism which is just not enough to categorize a drug. To categorize a drug according to the framework document, you look at the use pattern, we look at the appropriate classes or similar classes --- risk assessment would be necessary to categorize the drug.

DR. EWERT: But the way the framework document is written now, that categorization has to take place before the pre-approval study can be ---

DR. RIDDEL: Can we say only extenuating circumstances (changes in human medicine or NARMS data) would alter this categorization later in the process? So what you don't want is for a category II compound for some reason, the day you are getting ready to submit the package, then all of a sudden it changes, becomes a category I.

DR. EWERT: Right.

MR. MUSER: The framework document at the moment --- gives you an idea of what type of or the extent of studies or the extent of --- to do depending upon your category. If you do it by the end of the day I think it comes back --- complete

picture. ---

One could then revise the categorization, the official categorization and confirm it or change it.

DR. EWERT: Well, that is fine. You could just say something like final categorization must be confirmed subsequent to completion of pre-approval studies.

MR. MUSER: Subsequent to completion of the risk assessment.

DR. EWERT: Well, whatever.

DR. SHRYOCK: In slide 3 we already have a statement that gets into this and then says: "Not all uses and indications for all antimicrobials will require pre-approval studies." You could put another bullet on there that says depending upon categorization or pending categorization or something like that.

It links that concept but it doesn't get too specific. We can't be so certain today about how the --- you acknowledge it but don't go much further than that.

CO-CHAIRPERSON HESLIN: That would satisfy your concerns?

MR. MUSER: Oh, yes. That is fine.

DR. SHRYOCK: --- I was looking for Tom's version.

DR. RIDDEL: So, what is there?

DR. SHRYOCK: Just put something to the effect not

all uses and classes of antimicrobials require the same pre-approval studies as determined via categorization criteria.

DR. SHRYOCK: Right. Then put that into parenthesis criteria to be determined.

MR. BIENHOFF: Is there as fare --- as far as categorizing --- CVM ---

DR. SHRYOCK: I don't know what those parameters would be. I don't know if anybody knows that answer.

MR. BIENHOFF: I guess the point is to try to avoid some of the ---

DR. SHRYOCK: The only way that you will actually get a categorization changing from say a 2 to 1 would be through your post-approval monitoring --- rising to a sufficient level of concern. --- after the fact.

MR. BIENHOFF: Right.

DR. SHRYOCK: So in essence, what difference does it make if it then becomes a category I ---

Does that make sense?

MR. LUCAS: Tom, might did not find some unexpected cross-resistance ---

DR. SHRYOCK: Through your pre-approval testing that would relate it to a category I drug ---

MR. MUSER: Even after approval --- will not really

have an impact on your pre-approval study because it is --- this would have a heavy impact on --- mitigations from these thresholds. --- pre-approval deja vu.

MR. LUCAS: The point I was making though was if you were in your pre-approval testing program looking for instance at cross-resistance with this drug. And some unexpected set of cross-resistance showed itself, would one of those drugs being a category I drug, then it is immediately pulled up. So that would be a way, during the pre-approval testing, for the category to change.

DR. SHRYOCK: That is why you do studies.

DR. PETRICK: How significant is categorization? I guess I am having trouble right now with what we are proposing to do and how the data are to be used. What is the categorization drive? Will somebody help me with that again?

I mean if we are saying categorization is going to impact or what studies ---

MR. MUSER: I think it is more than that. If I recall it correctly, --- but I believe there is a camp in the scientific community that says that categories should not be approved for veterinary use period.

So from that point of view it would be worth it to --- if they want to go through with it to show that yes it did, --- initially isn't that category --- should be taken into

another one and it can't be approved?

DR. PETRICK: Yes. And I guess that's it. Unless something in the Center has changed, I believe the idea is that even vancomycin could be approved as a food additive for chickens if the --- that is kind of like the --

MR. MUSER: ---

DR. PETRICK: Yes, okay.

MR. MUSER: And because it is a ---

DR. PETRICK: Right. Okay.

MR. MUSER: ---

DR. PETRICK: Yes. And I guess that is what I am wondering. Have we gotten to the point now that categorization isn't as critical as it was at one point?

MR. MUSER: In our mind it is ---

DR. RHODES: Well, wasn't it yesterday that the CDC was basically saying that no category I drugs would be ---

DR. SHRYOCK: I think ---

DR. RHODES: But he said specifically no category I drugs could be used as feed additives. --- So I am looking at it from that point of view, obviously. --- which category a drug is in is going to drive ---

CO-CHAIRPERSON HESLIN: Just a time check. I think we have about 20 minutes more to go to get Gatz ready.

The good news is, if I am reading that right there

is about 13 slides that there seems to be substantial agreement on.

DR. RIDDEL: I think I had some blank ones at the end.

What do I need to do to craft the first point in this to what you want?

DR. GOOTZ: Isn't that already obvious --- from the framework document?

DR. SHRYOCK: --- but why does it mean ---

DR. GOOTZ: --- consistent with the framework document.

DR. SHRYOCK: --- state the obvious ---

DR. GOOTZ: Can I ask you a question? Where are we in this outline?

DR. RIDDEL: I think we had gone back when Kathy asked about categorization.

DR. GOOTZ: Oh, okay.

DR. RIDDEL: But we really were at point 9. We used seven and eight. Nine brought the discussion of categories and we put in a couple of slides. I guess we are now back to looking at 10.

Based on a couple of questions that were presented in the agenda, should the group comment on use of sentinel or surrogate organisms or just skip that? We did have a

discussion about sentinel organisms.

DR. GOOTZ: Wouldn't that be more appropriate for post-approval surveillance in part, later on? How to? How are we actually going to do that? It may not be needed to be ready now.

DR. EWERT: Well, it looks like the whole direction for the pre-approval studies is getting out of the animal and mostly in vitro studies here. And so the whole idea of sentinel organisms was, in animal studies, whether they were pre-approval or post-approval. But it looks like we don't have to make animal studies pre-approval.

So I would agree with what you are saying Tom, that maybe a post-approval issue --- but it is still something we need to make a comment about. I personally feel very strongly about that ---

DR. RIDDEL: So do you feel strong that they should or shouldn't be used?

DR. EWERT: I don't feel that it is an adequate representation to what is going on --- unless we can show some correlation between the percent --- food-borne pathogen.

MS. HARRIS: I would like us to have a comment on both sentinel organisms and dose optimization --- they were --- I think we reached a concurrence ---

DR. RIDDEL: So have several slides on what pre-

approval studies may include. Does that cover what you want to include in pre-approval studies? And do we go with the next vein as to working into a post-approval monitoring program?

Or how do we being to put information about sentinel organisms, optimum dosing, things like that?

DR. EWERT: Well, it looks like to me by the nature of the studies that we could put up here --- pre-approval. Those items are no longer an issue.

DR. RHODES: ---

DR. EWERT: Pardon me?

DR. RHODES: Or they are not on the table. ---

DR. EWERT: Right.

DR. RIDDEL: Should we address them and speak to why they are not included in our proposed pre-approval package and why we don't believe they have a place there and why they might have a place somewhere else, but why they don't belong here?

DR. EWERT: I think we can give our opinion. But somehow that will be your job Gatz, to bridge -- I mean why you are talking about it, but those aren't factors in the study --- but it would be nice for this group to go on record with what we think.

Because just because we think, this group believes, the studies should be done in vitro or through literature, doesn't necessarily mean that that is what the agency is going

to come up with. So, there are different pieces of this that they may pull out as far as recommendations.

So I think it is still valid to talk about it. You just have to give a caveat or two.

DR. VAUGHN: One thing you might do Gatz, is just say --- consider -- sentinel organisms are considered as optimization as potential pre-approval information that we feel should not be included for the following reasons.

Those reasons may apply to both pre-approval and post-approval ---

MR. BOETTNER: I think we say it when we discuss the design of concept studies --- study concepts or study models of this --- but you still should do probably some in vivo studies in the context of pre-approval studies.

DR. EWERT: But that is not what we are saying here. Other than pharmacokinetic data, many of those studies that are being described up there are laboratory studies.

I don't disagree with what you are saying. But I am saying that is not what we are saying as a group.

DR. GOOTZ: --- PK/PD --- I think we say if why would a nice AUC number be relevant to the selection of resistant zoonotic pathogens --- they wouldn't necessarily ---

MR. BIENHOFF: --- as far as the mechanism goes that is development of resistance --- how you are treating the

animal may --- I think the AUC data --- antimicrobial.

DR. GOOTZ: Somewhere, I think on the previous slides --- something about --- levels of drug in feces --- so this is really the systemic PK/PD issue that would bear upon the selection of resistance in zoonotic pathogens.

It would be whether or not that drug, regardless of its PK is excreted in feces. Therefore, we should know something about the level of our drug in the feces of our indicator ---

DR. EWERT: But what does that have to do with a sentinel organism?

DR. GOOTZ: I don't know.

DR. EWERT: I mean that is what the question is. If you go back, Gatz can you just go back and look at the slide where the group has suggested the different study types and -- I can's see in any of those studies --- sentinel --

DR. RIDDEL: In this presentation or the other one?

MR. : --- animals ---

DR. EWERT: But NARMS doesn't have sentinel organisms.

MR. : --- they are looking at salmonella, generic E. coli, generic enterococci, campylobacter.

DR. EWERT: But I am not talking about -- I am talking about sentinel the way Dr. Walker talked about it, the

way the agency is now looking at it. Where as generic E. coli is representative of food-borne pathogens. That is the type of sentinel I am talking about. And I don't see this.

CO-CHAIRPERSON HESLIN: Was it on a slide or on the earlier list?

DR. EWERT: No, it was on this slide or the previous slide.

DR. PETRICK: It is this slide right here.

DR. EWERT: Or is it the other slide that says pre-approval ---

DR. PETRICK: But I think again, where we were coming from is that the information is good to have. The PK/PD, the fecal levels, but I think the time to collect it is up front, but the usefulness may not be apparent until we get into post-approval.

But I think you want to have it up front so it is there to be useful if a problem develops or if you start going down the road of mitigation, one of the things you can say, well a mitigating factor isn't going to be the level that is being excreted if it is never excreted in the feces. So, you move that off since that is not a place you are going to go.

You may say well let's look at the area under the curve to address the resistance issue that is developing. Maybe if we increase that or maybe --- can be higher and we can

adjust the dose ---

I think it is information that we can collect that is efficacy in one stage, post-approval maybe it becomes something else.

DR. GOOTZ: Well, it is part of the baseline data, but again I think we are focused on safety --- selection of fecal zoonotic pathogens. The only relevant part of that is number one, whether the drug is out --- number two, it would be nice to know fairly early on how much is there.

DR. PETRICK: Right. And I guess that would be the degree of binding, right?

DR. GOOTZ: Yes. Oh, and the binding ---

DR. PETRICK: Right.

MR. SCHMID: But this doesn't tell you anything about the --- it could be binding to bacteria. I think the recommendations of the --- susceptible indicator organism --- could be a very meaningful tool to --- potential side effects from ---

DR. GOOTZ: So you are proposing pre-approval in vivo studies ---

MR. BIENHOFF: --- as in contrast --- if you have a drug that is excreted --- it may or may not --- again, it all depends on the compound.

DR. GOOTZ: I think it is a --- point. It is just

hard to practice in a pre-approval study. But again, --- but in terms of so far as selecting resistance pathogens, I am not aware of ---

MR. BIENHOFF: All I am saying is this is just a data plan.

DR. RIDDEL: As far as the concept of sentinel organisms. I heard the group just saying today, especially with some input from Kathy, that they don't provide a valid comparison for human food-borne pathogens, or at least that information is not there in literature, right?

And we didn't put in our list of information to put in the pre-approval package anything about sentinel organisms. Unless you have changed your mind, then it obviously is a topic that has been discussed at CVM and we probably need to justify why we considered this but did not include it.

DR. PETRICK: And I think you have captured it ---

DR. EWERT: That looks good to me.

DR. RIDDEL: That is good enough? Okay. The concept of optimal dose. That is not in the pre-approval package. Why?

DR. GOOTZ: that may need to be determined and modified and later on after field studies. --- make your best judgment on the dose that should be used. --- the sponsor may find that the dose isn't high enough or it is too high.

DR. RHODES: I think you have to be very careful there because we talk about modifying the dose post-approval. But it is just not practical from a sponsor's point of view. You would have to go back and repeat your 1-3-5 studies on the target animal. You would have to redo all your residue studies to include them --

DR. PETRICK: Maybe what we should look at is then benefits gained. The system that we have right now establishing flexible dosage based on efficacy and safety is the best system that we have. And any benefit in modifying that or working toward an optimal dose from a resistance standpoint isn't as critical as that flexibility for the practitioner.

I think we go back to right now we say the minimal dose for efficacy from the field and a maximum dose based on safety from a target animal and residue sampling. And I think that is a good place to be and I don't see anything that we have discussed so far from resistance that should make us turn away from that process.

That was a harm group --- in the system. Both receiving with the industry and with the practitioners. I think everybody believes there is a great deal of benefit from that flexible dosage scheme. So right now, I don't think we want to modify that based on resistance when we don't even know

what the right dose would be to prevent or to limit resistance development.

I don't know how we capture that, but I --

DR. GOOTZ: I think --- misleading when I said --- consideration, but that also ---

MS. HARRIS: I guess I would like to propose a single statement to deal with the issue. I don't think we should call it optimum dosage, we should call it dose optimization --- and I think we should say ---

MR. LADELY: It has a place. Dose for resistance is good for evaluating risk. In risk assessment it has a place. In therapeutic treatment of animals it does not. --- practitioner judge what drug should I use, maybe that risk assessment should come into play. But as far as having any bearing on pre-approval, I don't believe it has a place.

DR. VAUGHN: I don't think we can make a judgment on what would be an optimum dose ---

DR. WALKER: --- lot's of studies out there showing that there is a direct correlation ---

DR. GOOTZ: I think those were --- inadequate levels in the lung ---

DR. WALKER: --- there are studies out there --- the AUC values are good --- selecting for resistant organisms.

DR. GOOTZ: Right, but we are --- that you are going

to hold responsible for salmonella, campylobacter, E. coli. So, a PK --- systemic therapy ---

DR. WALKER: --- we really don't look at the serum concentration --- mucus secretions are very high ---

DR. GOOTZ: I am not aware of direct studies that have been identifying or concerned with the --- campylobacter is becoming susceptible to macrolides, but we are not going there ---. I am not trying to argue, I am just trying to say that what are safety issue ---

DR. WALKER: What I am saying --- but also maximizes resistance ---

CO-CHAIRPERSON HESLIN: We are running out of time. I wonder if there is some way to bring this to closure, possibly, what is being proposed up here.

DR. RIDDEL: What about that third point?

DR. VAUGHN: There are a lot of ---

CO-CHAIRPERSON HESLIN: Well, is this too much to bite off?

DR. RIDDEL: You really haven't said anything about why dose optimization has a place in the pre-approval package with those first two points.

MR. BOETTNER: But, --- no study models available in pre-approval studies --- resistance development, so how can you determine the optimum dose ---

DR. VAUGHN: Something to the order of the variation, the variables that are encountered in a field situation are such that it is difficult to realistically design an adequate number of studies to provide ---

CO-CHAIRPERSON HESLIN: I see several heads nodding at that one. Can you live with that?

DR. RIDDEL: Say it again.

DR. VAUGHN: Due to variables involved in a field use situation --- design an adequate number of studies to provide ---

DR. RHODES: How about just to assess resistance development?

DR. VAUGHN: Relative to resistance development.

DR. RHODES: I think it is important to say, just as you alluded to the practical field use of these antibiotics, even if we as an industry/government organization go out to the practitioner and say you know, if you use twice as much of this drug and you have twice as long a withdrawal period, it is going to be better because we won't develop resistant pathogens for humans.

But we know that half of the amount is efficacious. What are the cowboys going to use? They are going to use just enough drug in order to get that animal feeling better and they are really not going to care much about development of

resistant pathogens.

So they are going to take that bottle and they are going to read the dose. They are going to say you know what, Joe Schmoe down the road says if I use half as much of this it works out just as well for my cows, and they are going to use half as much.

Realistically that is the kind of thing that is going to happen in the field. And so it becomes a very theoretical exercise to set a dose based on resistance development.

DR. VAUGHN: You know, Bob's right in terms of in a given situation as a general rule, the higher the dose the higher --- less the likelihood of the development of resistance. But, you also have to look at the environment in which the animal is treated and the impact on the bug.

Because it is not --- one concentration of drug that any particular bug is exposed to. --- zero. So the potential for resistance --- there are a lot of factors to include in the situation to optimize the dose.

Bob's right. I mean I don't want to give you the impression that Bob's not right about the C-max thing, but it is situational. ---

CO-CHAIRPERSON HESLIN: Okay. You can live with that one?

DR. PETRICK: That looks good.

DR. RIDDEL: Steve, I don't know what the word inferential means so I can't use it.

DR. VAUGHN: That is all right. That is fine. It is like pivotal.

DR. RIDDEL: I am all over that one.

DR. GOOTZ: It has a lot of meanings to a lot of different people.

CO-CHAIRPERSON HESLIN: Are there any other bullets that we haven't looked at?

DR. RIDDEL: Yes.

MR. BOETTNER: About number 16 --

DR. RIDDEL: Yes?

MR. BOETTNER: I think with our pre-approval studies we do generate a lot of information about resistance development techniques and we also said that we generate baseline data. But looking ahead for post-approval --- thresholds that set forth specific compounds --- how can we determine which of the compounds we used contributed to the resistance development?

DR. RIDDEL: Tough one.

MR. BOETTNER: Very tough. But we have to assure -- but we are saying that we are setting also basic information for post-approval studies. Post-approval studies, this is

resistance monitoring, while in efficacy it means setting stress --- and mitigations.

Does this really relate to a product? So what needs to be done to identify this product or this class ---

DR. GOOTZ: So the question is then --- post-approval surveillance --- that would be the answer to that today.

DR. SHRYOCK: I think it is a good point, but I am not sure how to fit it in a pre- situation.

MR. BOETTNER: It doesn't really fit into that I don't think. I think it is very, very important --- we may develop a lot of information out of pre-approval studies which then does really not help us with the overall objective. ---

DR. PETRICK: But I don't think there is anything we have proposed today that is going to -- that is limiting or negative from the standpoint of it is not good information to have.

I agree with you because there is that the factor, but I think for right now -- I think we have to address it at another context when we can focus it on post-approval. It could be the same thing. --- how is post-approval monitoring done and when we take these examples they need to be identified in such a manner that you can compare it to a farm.

--- trace it that closely so you can look at where

did that organism or where did those organisms come from. Is there a pattern reached from that research. And then focus on --- I think that is how you focus it then.

If the idea is to catch things early, --- go all the way to the farm level and the individual producer of that ---

DR. RIDDEL: There were some significant comments in the other document about use patterns and there were some good comments made about use patterns. Do you want to put any comments in here?

Do we just want to stop at the pre-approval package or do you want to provide some insight that we have put together over the last day as far as how some of this one, is either more appropriate for the post-approval phase, or how maybe the pre-approval information should be utilized in the post-approval phase?

DR. GOOTZ: ---- post-approval you are probably talking about another four or five hours ---

MR. BIENHOFF: I guess ---

DR. PETRICK: The only other question I wonder if we need to --- preliminary slide some where. Because we do talk at some length about it can't be a one-size fits all and have we captured that in one of the early slides about flexibility approaches based on the individual product. ---

If we haven't captured that I think we should. If

we have, then I think we have got --- I couldn't remember.

DR. GOOTZ: Didn't we capture that in the discussion on categorization ---

DR. PETRICK: Well, in the course of this we say you have to kind of tailor it for one of your studies and your approach has to be tailored and one of the things we talked about is making sure there is enough flexibility in the process that both the Center and the sponsor can work through it.

As long as we have captured as something we discussed then I think we have gotten the rest. The only other salient point I saw in those last five ---

MR. BOETTNER: --- means is that we can ---

DR. RIDDEL: Very quickly we will run through what we have and if you think that there is something that we need to add that is pertinent to one-size doesn't fit all, say it.

And I can go back if I am going too fast.

DR. PETRICK: Oh, there we go. It is that first point ---

DR. RIDDEL: Okay.

CO-CHAIRPERSON HESLIN: And we can quit while we are head?

MR. BOETTNER: I have a question.

DR. RIDDEL: Yes.

MR. BOETTNER: The original list of questions you

made from our brainstorming session, will you provide a printout of this as well for the participants of this breakout session?

CO-CHAIRPERSON HESLIN: I think we can do that. I will check on that.

DR. RIDDEL: Well, if you remember on that we have one comment, and I think Dr. Mevius pointed this out, pertinent to food-borne pathogens had two positive comments and no negative comments. So I don't know that that is good working material. Maybe for your interest, but I am not sure it needs to --

MR. BOETTNER: What would be a basis for at least the slide or presentation --- this afternoon --- comments which ---

CO-CHAIRPERSON HESLIN: I will check to see whether we can get copies of that if you just want to take it for your own information.

The room needs to be apparently set up for the next session, so we are really pretty much out of time. But do you have a comment or question just to close it out?

DR. SHRYOCK: I think the one thing that we were going to circle back around on was how these studies would be interpreted or used. It was at that discussion around the word pivotal.

What that particular aspect meant. When we generate all of this data, how is that to be used. I don't have a quick bullet point to lay out here.

DR. PETRICK: Maybe that is a good place to put it, right there in the transitioning to a post-approval --- and the comment is that the pre-approval data lays the foundation for transitioning into the post-approval monitoring program. Maybe that is sufficient to address it.

DR. GOOTZ: Also, I think that we are in agreement that all of this, this whole package of pre-approval microbiology that we talk about, in and of itself is pivotal, it is important. But, that individual microbiology studies cannot be perceived as pivotal.

Let me rephrase that. We all agree that all of these things are supportive. We all agree we are going to resistance emergence in vitro. We are going to do good field studies, MICs. I think gene transfer, but I am getting fuzzy. Other things that we put on that slide.

That unit as a whole, all of that data is important to establish baselines pre-approval. In that sense, from the organization's point of view you said you would use the word pivotal. In the sense that if you don't have them at all we don't go forward.

But, are we in agreement to say that but we cannot

use a single study such as a result from a gene transfer or the result from a single selection of resistance frequency with one organism to be designated as pivotal?

DR. PETRICK: I think to stay away from the --- to not get --- pivotal. I think what we are getting at is the results do not lead to pass/fail decisions.

DR. GOOTZ: One result itself. I mean the whole package could lead to that, if it is a crummy package. If all of the information is bad.

DR. PETRICK: Yes, but the only way the information is bad is if it is not done --- reproducible --- product actually is. ---

DR. GOOTZ: Well, my position is that there be somebody looking at it and say that we have new drug X which belongs to macrolides just for the sake of argument. The selection of resistance in one study, one microbiology study which is part of an entire large package, indicates the frequency is one times 10^{-4}. One study, one organism.

Is that sufficient in and of itself to really put that drug on hold from the resistance perspective. I would hope not. I would hope that what we are talking about when we say important, pivotal, whatever studies is the entire package.

Because obviously it should be of high quality. It should contain, I think we agreed on a set number of things.

We shouldn't be trying to skip things for a short-cut. But that the importance of that package is really looking to the agency to look at it totally, but not dissect it and say one result in and of itself is sufficient to, and I won't use the P word, to stop further consideration of that compound. One of those subheadings of microbiology such as gene transfer or selective resistance.

CO-CHAIRPERSON HESLIN: I need to interrupt to say that we are out of time. There is a public comment period after the discussion panel. So there will be --

DR. VAUGHN: We need to fix the last bullet ---

I think what your concern is, is that any result, not necessarily a single study --- to make a pass/fail determination because the --- the idea is ---

DR. GOOTZ: --- if everything else is actually very reasonable having --- organisms that have a high --- I think that would be sensible if that is what we want to try to put.

(Breakout Session Concluded at 12:25 p.m.)